Ultrasound in Med. & Biol., Vol. 40, No. 10, pp. 2404–2414, 2014

0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2014.04.013

● *Original Contribution*

# MONITORING AND STAGING ABDOMINAL AORTIC ANEURYSM DISEASE WITH PULSE WAVE IMAGING

Sacha D. Nandlall,* Monica P. Goldklang,† Aubrey Kalashian,* Nida A. Dangra,* Jeanine M. D'Armiento,† and Elisa E. Konofagou‡

*Department of Biomedical Engineering, Columbia University, New York, New York, USA; †Department of Medicine, Columbia University, New York, New York, USA; and ‡Departments of Biomedical Engineering and Radiology, Columbia University, New York, New York, USA

(*Received* 16 *October* 2013; *revised* 31 *March* 2014; *in final form* 21 *April* 2014)

**Abstract—The abdominal aortic aneurysm (AAA) is a silent and often deadly vascular disease caused by the localized weakening of the arterial wall. Previous work has indicated that local changes in wall stiffness can be detected with pulse wave imaging (PWI), which is a non-invasive technique for tracking the propagation of pulse waves along the aorta at high spatial and temporal resolutions. The aim of this study was to assess the capability of PWI to monitor and stage AAA progression in a murine model of the disease. ApoE/TIMP-1 knockout mice (N = 18) were given angiotensin II for 30 days via subcutaneously implanted osmotic pumps. The suprarenal sections of the abdominal aortas were imaged every 2–3 d after implantation using a 30-MHz VisualSonics Vevo 770 with 15-$\mu$m lateral resolution. Pulse wave propagation was monitored at an effective frame rate of 8 kHz by using retrospective electrocardiogram gating and by performing 1-D cross-correlation on the radiofrequency signals to obtain the displacements induced by the waves. In normal aortas, the pulse waves propagated at constant velocities (2.8 ± 0.9 m/s, $r^2$ = 0.89 ± 0.11), indicating that the composition of these vessels was relatively homogeneous. In the mice that developed AAAs (N = 10), the wave speeds in the aneurysm sac were 45% lower (1.6 ± 0.6 m/s) and were more variable ($r^2$ = 0.66 ± 0.23). Moreover, the wave-induced wall displacements were at least 80% lower within the sacs compared with the surrounding vessel. Finally, in mice that developed fissures (N = 5) or ruptures (N = 3) at the sites of their AAA, higher displacements directed out of the lumen and with no discernible wave pattern ($r^2 < 0.20$) were observed throughout the cardiac cycle. These findings indicate that PWI can be used to distinguish normal murine aortas from aneurysmal, fissured and ruptured ones. Hence, PWI could potentially be used to monitor and stage human aneurysms by providing information complementary to standard B-mode ultrasound.**
**(E-mail: ek2191@columbia.edu)** 

*Key Words:* **Abdominal aortic aneurysm, Fissure, High-frequency imaging, Mice, Motion estimation, Normalized cross-correlation, Pulse wave velocity, Regional pulse wave, Rupture, Speckle tracking, Ultrasound imaging.**

## INTRODUCTION

The abdominal aortic aneurysm (AAA) is a common vascular disease characterized by a localized ballooning or dilation of the abdominal section of the aorta, often as a result of a localized weakness in the vessel wall (Crawford et al. 2003). Depending on the age group, AAAs are estimated to occur in 1.3% to 12.5% of men and up to 5.2% of women, with prevalence rising in older age groups (Go et al. 2013). The leading cause of AAA-induced death is severe internal bleeding after a sudden rupture of the vessel wall within the sac of the aneurysm. Even with immediate medical attention, more than 85% of ruptured AAAs eventually prove fatal, and approximately half of those afflicted die even before reaching the hospital (Forsdahl et al. 2009; Patterson et al. 2008). In the developed world, ruptured AAAs are a leading cause of death in males 65–85 years old and are responsible for up to 2% of deaths in the entire population (Sakalihasan et al. 2005; Urbonavicius et al. 2008), including more than 10,000 deaths annually in the United States (Murphy et al. 2013), as well as more than 7000 deaths annually in England and Wales (Stather et al. 2013).

Abdominal aortic aneurysms are typically diagnosed with non-invasive imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT) and 2-D ultrasound B-mode imaging (Crawford et al.

Address correspondence to: Elisa E. Konofagou, Department of Biomedical Engineering, Columbia University, 1210 Amsterdam Ave., ET 351, MC 8904, New York, NY 10027, USA. E-mail: ek2191@columbia.edu

2003; Sakalihasan et al. 2005). However, screening for AAAs is challenging, because most patients are asymptomatic until the aneurysm ruptures (Patterson et al. 2008; Sakalihasan et al. 2005) and relatively few definitive risk factors have been identified (Crawford et al. 2003; Manning et al. 2002). As a result, only the United States, United Kingdom and Sweden have implemented standardized AAA screening procedures nationally (Stather et al. 2013). Moreover, even when an AAA is detected, the options for treating it are currently open surgery and endovascular repair (Brewster et al. 2003). Both procedures only performed only when the risk of AAA rupture is deemed to be greater than the risk of mortality from post-operative complications (Patterson et al. 2008), which is especially significant in the case of open surgery (Manning et al. 2002). The metric that is currently used for assessing risk of AAA rupture is the maximum transverse diameter of the aneurysm (Stather et al. 2013; Urbonavicius et al. 2008). Unfortunately, this criterion is a poor predictor of the actual likelihood of rupture (Brewster et al. 2003; Choksy et al. 1999; Vorp et al. 1998) and does not have a sound physical or theoretical basis (Allison et al. 2008; McGloughlin and Doyle 2010). This means that currently, many small AAAs that are deemed too small to treat end up rupturing regardless, and several patients with large but stable AAAs are subjected to unnecessary surgery.

A better means of assessing rupture risk is to measure localized changes in the material and mechanical properties of the vessel. Such parameters play a greater role than diameter in determining whether or not a rupture occurs, notably because their values change depending on the amounts of collagen and elastin present in the vessel wall (Haskett et al. 2010; Lasheras 2007). In particular, multiple clinical studies have established that arterial stiffness as a biomarker of all-cause and cardiovascular disease-related mortality (Adji et al. 2011; Hamilton et al. 2007; Zoungas and Asmar 2007). In the clinic, carotid-femoral pulse wave velocity (PWV) is currently the gold standard metric of arterial stiffness (Nemes et al. 2011; Laurent et al. 2006; Sutton-Tyrrell et al. 2005). Every cardiac cycle, the ejection of blood from the left ventricle of the heart sends a pulse wave propagating throughout the arterial tree, which gives rise to the natural pulsation of the arteries and induces a displacement wave in the vessel walls (Fung 1996). The velocity of this wave, that is, the PWV, is mathematically linked to the radial stiffness of the vessel via the Moens–Korteweg equation (Korteweg 1878; Moens 1877), which is derived from Newton's second law and states that the Young's modulus of the vessel wall is proportional to the square of the PWV (under certain simplifying assumptions, including a homogeneous, perfectly cylindrical vessel, as well as small wall displacements relative to the baseline vessel diameter). As with arterial stiffness, PWV has been found to be an effective biomarker for several diseases, particularly in hypertensive patients (Lehmann 1999; Mitchell 2009).

Various methods have been used to image pulse wave propagation, including pressure catheterization (Segers et al. 2005), phase contrast magnetic resonance imaging (MRI) (Kraft et al. 2001; Macgowan et al. 2002) and pulsed Doppler imaging (Hartley et al. 1997; Eriksson et al. 2002; Rabben et al. 2004). The most common method is applanation tonometry (Laurent et al. 2006; Lehmann 1999), in which PWV is computed by measuring the time delay between the pulse pressure waveforms at two different points in the circulation (typically the carotid and femoral arteries) and dividing the estimated distance between these two points by the measured time delay. However, because this technique provides only an average global PWV and can be affected substantially by variations in the estimated arterial path length (Sugawara et al. 2010), it is unsuitable for measuring highly localized changes in stiffness that would indicate the onset of an aneurysm.

Pulse wave imaging (PWI) is a non-invasive, ultrasound-based technique for visualizing and tracking the propagation of pulse waves along the arterial wall at high spatial and temporal resolutions. PWI has been validated *in silico* using simulations (Shahmirzadi and Konofagou 2012), *in vitro* using phantoms (Shahmirzadi et al. 2013; Vappou et al. 2010), *ex vivo* with canine aorta (Shahmirzadi et al. 2013), *in vivo* with mice (Fujikura et al. 2007; Luo et al. 2009; Pernot et al. 2007) and clinically in humans (Li et al. 2013; Luo et al. 2012). The high resolution of PWI means that it can provide localized maps of PWV, thereby allowing for the identification of subtle changes in the pulse wave propagation patterns, as well as regional variations in vessel wall stiffness. This capability could allow PWI to identify emerging abnormalities in the vessel that act as precursors to aneurysm formation and are not visible or easily detectable with standard imaging modalities such as ultrasound B-modes.

The objective of this study was to investigate the feasibility of using PWI to monitor and stage the progression of AAAs *in vivo*. To this end, a murine model of gradual AAA development based on the infusion of angiotensin II in ApoE/TIMP-1 knockout mice was used in this study (Lemaître 2002; Luo et al. 2009; Manning et al. 2002). Although PWI can be applied in humans, using a murine model enables disease progression to be monitored over its entire duration at many closely spaced time points. Additional advantages of murine aneurysms for the purposes of this study are that they can be instigated in a controlled fashion, require